BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

198

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 49/02, 43/00 — A1

(11) International Publication Number: WO 94/22496

(43) International Publication Date: 13 October 1994 (13.10.94)

(21) International Application Number: PCT/US94/03389

(22) International Filing Date: 29 March 1994 (29.03.94)

(30) Priority Data:
08/040,739 31 March 1993 (31.03.93) US

(71) Applicant: MALLINCKRODT MEDICAL, INC. [US/US]; 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).

(72) Inventors: BRODACK, James, W.; 3827 Kentucky Derby Drive, Florissant, MO 63034 (US). DEROSCH, Mark, A.; 1762 Winding Glen Drive, St. Charles, MO 63303 (US). DEUTSCH, Edward, A.; 12805 Maryland Estates Court, Maryland Heights, MO 63043 (US). DEUTSCH, Karen, F.; 12805 Maryland Estates Court, Maryland Heights, MO 63043 (US). DYSZLEWSKI, Mary, Marmion; 12221 Autumn Dale Court, Maryland Heights, MO 63043 (US).

(74) Agents: MCBRIDE, Thomas, P. et al.; Mallinckrodt Medical, Inc., 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).

(81) Designated States: AU, BR, CA, CZ, FI, HU, JP, KR, NO, PL, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: RADIOPHARMACEUTICAL FORMULATIONS HAVING NON-STANNOUS REDUCTANTS

(57) Abstract

The present invention relates to novel radiopharmaceutical imaging agents having non-stannous reductants. Metallic compounds, such as Cu(I), Cu(II), Co(II), Fe(II), Sn(O), Zr(O), Cr(II) and Zn(O), will act to effectively reduce radionuclide containing solutions. Several non-metallic compounds, such as acids in general, dithionite, formamidine, formamadine sulfinic acid, phosphite, hypophosphite, dithiotreitol, hydrochloric acid, and borohydric acid may also be used to reduce radionuclide containing solutions. Moreover, it has been discovered that several agents, such as phosphines, sulfhydryl compounds, phosphites, thiols, thioethers, borates, borocyano groups, ascorbates and gentisates efficiently reduce radionuclide containing solutions and complex with the radionuclide at the same time. The present invention also relates to kits for forming radiopharmaceutical imaging agents, such kits including non-stannous reducing agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

RADIOPHARMACEUTICAL FORMULATIONS HAVING NON-STANNOUS REDUCTANTS

Background

The present invention relates to novel radiopharmaceutical imaging agents having non-stannous reductants. The present invention further relates to kits for forming radiopharmaceutical imaging agents, such kits including non-stannous reducing agents.

Several non-invasive methods of imaging skeletal structures, and body organs and tissues have been developed over the past decades. These methods are based on the tendency of the particular skeleton, organ or tissue to concentrate certain chemicals which may be detectable, such as through the use of scintiphotography or radiation detection. The use of radiopharmaceutical imaging agents in imaging skeletal structures, organs and tissues, is well known in the fields of biological and medical research as well as diagnostic evaluation procedures. Metal-based radiopharmaceuticals, such as those based on technetium have been found to provide particularly useful images of skeletal structures, and body organs and tissues from which diagnostic information may be obtained. More particularly, radiopharmaceuticals based on technetium 99m have been used successfully as diagnostic imaging agents.

In addition, metal-based radiopharmaceuticals, such as those based on rhenium have been found to be useful as therapeutic agents in the treatment of various diseases. More particularly, radiopharmaceuticals based on rhenium 186 or rhenium 188 have been used sucessfully as therapeutic agents.

The radiopharmaceutical agents generally include a metal radionuclide, various ligands for binding the

radionuclide to the desired skeletal structure, organ or tissue, reducing agents, stabilizing agents, carriers and delivery vehicles suitable for injection into, or aspiration by a patient, etc.

Because of the relatively short half-lives of the metal radionuclide used in the radiopharmaceutical agent, it is desirable to provide the non-radioactive components of the agent as a kit to which a radionuclide containing solution may be added to form the agent. In particular, a radionuclide generator may be employed in a known manner to obtain a radionuclide which may then be combined and reacted with the contents of a kit which contains appropriate radiopharmaceutical forming components. For example, when forming a technetium imaging agent, a pertechnetate solution may be obtained from a technetium generator. The pertechnetate solution may then be combined and reacted with the components of a kit containing the other materials and agents necessary for forming the radiopharmaceutical agent.

A reducing agent is a necessary component of many radiopharmaceutical kits, the reducing agent acting to reduce the radionuclide containing solution, such as a pertechnetate solution, to obtain the final radiopharmaceutical agent. A reducing agent must be included in kits for the formation of technetium radiopharmaceuticals. Stannous ion is the most widely used reducing agent in kits for forming metal-based radiopharmaceuticals. This includes known kits for forming technetium 99m diagnostic agents for imaging the heart, kidney, lungs, and hepatobiliary system, as well as kits for imaging and therapeutic treatment of the brain and skeleton. However, the use of stannous ion as a reducing agent has several disadvantages generally arising from the

inherent problems related to the complicated solid and solution chemistry of stannous compounds. In particular, the stannous ion is often a "non-innocent" reducing agent which interferes with or is incorporated into the final radiopharmaceutical.

Therefore it is desirable to provide radiopharmaceutical forming kits which contain non-stannous reducing agents.

Objects Of The Invention

It is one object of the present invention to provide radiopharmaceutical formulations having non-stannous reductants.

It is another object of the present invention to provide kits for forming radiopharmaceutical agents, such kits including non-stannous reducing agents.

Summary Of The Invention

The above objects and others are achieved by providing a kit for forming radiopharmaceutical agents, wherein the kits include non-stannous reducing agents.

Detailed Description Of The Invention

The use of stannous ion as a reductant for preparation of radiopharmaceutical agents is well known. Therefore, stannous ion is commonly included as a component of kits for forming radiopharmaceutical agents, such as agents for imaging the heart, kidneys, lungs and hepatobiliary system and agents for imaging and therapeutic treatment of the

brain and skeleton.

However, the use of stannous ion as a reducing agent in the formation of radiopharmaceutical agents has several disadvantages. In particular, stannous compounds have inherent disadvantages associated with their complicated solid and solution chemistry. For example, stannous ion often acts as a "non-innocent" reductant and may interfere with the formation of the final radiopharmaceutical agent, or become incorporated into the final radiopharmaceutical agent.

It has been discovered that there are a number of pharmaceutically acceptable non-stannous reducing agents which do not possess the same disadvantages of using stannous ion as a reducing agent in the formation of radiopharmaceutical agents.

In particular, metallic compounds, such as Cu(I), Cu(II), Co(II), Fe(II), Sn(0), Zr(0), Cr(II) amd Zn(0), will act to effectively reduce a radionuclide containing solutions, such as pertechnetate solutions, to obtain the desired final radiopharmaceutical agent.

Further, several non-metallic compounds, such as acids in general, dithionite, formamidine, formamadine sulfinic acid, phosphite, hypophosphite, dithiothreitol, hydrochloric acid, and borohydric acid, may also be effectively used to reduce radionuclide containing solutions.

Moreover, it has been discovered that several agents, such as phosphines, sulfhydryl compounds, phosphites, thiols, thioethers, borates, borocyano groups, ascorbates, and gentisates, efficiently reduce the radionuclide

containing solution and complex with the radionuclide at the same time. This is very advantageous in reducing the number of components that must be included in kits for forming radiopharmaceuticals, and in simplifying the chemistry needed to produce the final radiopharmaceutical agent.

According to one embodiment of the present invention, a kit for forming a technetium myocardial imaging agent includes tris(3-methoxypropyl)phosphine (TMPP), as both a reducing agent and as a complexing agent. Further components, such as cuprous ascorbate, may also be included in the kit to increase radiopharmaceutical yield. Notably, it has been found that the addition of stannous ion to the kit actually reduces the product yield by forming reduced hydrolyzed technetium as a by-product.

In a further embodiment of the present invention, a kit for forming radiopharmaceutical imaging agents includes tertiary phosphines (PR_3) wherein the phosphine also acts as a ligand for the technetium complex. In particular, it has been discovered that $^{99m}Tc(VII)O_4^-$ may be reduced using a monodentate phosphine, such as, tertiary phosphines in the presence of a Schiff base ligand (L4). The kit may be a lyophilized kit containing the tertiary phosphine, the Schiff base ligand, and a buffer, but does not require ancillary reductants such as stannous ion, hypophosphite, or ascorbate to carry out the reduction reaction, if the technetium-99m generator eluant is degassed prior to its use. It is believed that the reduction reaction proceeds through a $^{99m}Tc(V)$ intermediate, such as $^{99m}Tc(V)(O)(L4)^+$, to ultimately form $^{99m}Tc(III)(L4)(PR_3)_2^+$, as a myocardial imaging agent.

In addition, in accordance with the present invention,

it has been discovered that hypophosphite ion $(H_2PO_2)^-$ may be used as an antioxidant and reductant in the formation of Tc-99m radiopharmaceuticals. The reduction potential for hypophosphite ion is comparable to ascorbic acid. Further, the oxidation product of hypophosphite is phosphite, PO_3^{3-}, which is totally innocuous in Tc-99m radiopharmaceutical preparations. Hypophosphite and phosphite are totally colorless, easy to analyze, lyophilizable, and injectable.

In another embodiment according to the present invention, it has been discovered that hydrogen phosphite (HPO_3^{2-}) may be used as an antioxidant and reductant in the formation of Tc-99m radiopharmaceuticals. The reduction potential for hydrogen phosphite is comparable to ascorbic acid. Further, the oxidation product of hydrogen phosphite is phosphate, PO_4^{3-}, which is totally innocuous in Tc-99m radiopharmaceutical preparations. Phosphite and phosphate are colorless, easy to analyze, lyophilizable, and injectable.

The foregoing has been a description of certain preferred embodiments of the present invention, but is not intended to limit the invention in any way. Rather, many modifications, variations and changes in details may be made within the scope of the present invention.

What is claimed is:

1. A kit for forming a radiopharmaceutical imaging agent which includes a non-stannous reducing agent.

2. A kit according to claim 1, wherein said reducing agent is a metallic compound selected from the group consisting of Cu(I), Cu(II), Co(II), Fe(II), Sn(0), Zr(0), Cr(II) amd Zn(0).

3. A kit according to claim 1, wherein said reducing agent is a non-metallic compound selected from the group consisting of acids in general, dithionite, formamidine, formamadine sulfinic acid, phosphite, hypophosphite, dithiothreitol, hydrochloric acid, and borohydric acid.

4. A kit according to claim 1, wherein said reducing agent is selected from the group consisting of phosphines, sulfhydryl compounds, phosphites, thiols, thioethers, borates, borocyano groups, ascorbates, and gentisates.

5. A kit according to claim 4, wherein said reducing agent is a mono-dentate phosphine.

6. A kit according to claim 5, wherein said reducing agent is tris(3-methoxypropyl)phosphine.

7. A kit according to claim 5, wherein said reducing agent is a tertiary phosphine.

8. A kit according to claim 5, wherein said reducing agent is hypophosphite ion.

9. A kit according to claim 5, wherein said reducing agent is hydrogen phosphite.

10. A kit according to claim 1, wherein said reducing agent is also a complexing agent for the radiopharmaceutical imaging agent.

INTERNATIONAL SEARCH REPORT

...national application No.
PCT/US94/03389

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 49/02, 43/00
US CL :424/1.11, 1.65
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.11, 1.65

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 3,749,556 (BARAK ET AL.) 31 July 1973. See the Abstract; column 2, lines 47-61; and column 3, line 68 bridging column 4, line 3.	1, 2
X -- Y	US, A, 4,208,398 (KUBIATOWICZ ET AL.) 17 June 1980. See column 6, lines 8-41.	1-4, 8 --- 9
X, P	US, A, 5,202,109 (FRITZBERG ET AL.) 13 April 1993. See column 16, lines 9-16 and column 19, lines 28-56.	1-4, 8
X	US, A, 4,925,650 (NOSCO ET AL.) 15 May 1990. See columns 5, lines 25-32 and lines 60-68.	1-3
X	US, A, 4,314,986 (RUDDOCK) 09 February 1982. See column 2, lines 16-26.	1, 2

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
26 APRIL 1994	01 JUN 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Diane Goodwin for JOHN M. COVERT Telephone No. (703) 308-0444

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/03389

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,957,728 (DEUTSCH ET AL.) 18 September 1990. See column 2, line 1 bridging column 3, line 30; column 4, lines 1-15; and column 5, line 55 bridging column 6, line 6.	1, 2, 4-7, 10
X	US, A, 5,069,900 (LINDER) 03 DECEMBER 1991. See column 3, lines 45-65, and column 4, lines 37-58.	1, 4-7
A	US, A, 5,112,594 (WOULFE ET AL) 12 May 1992.	

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US94/03389

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS Messenger

L1 = 1427 S 424/1.1/CCLS
L2 = 9 S 424/1.!!/CCLS
L3 = 1436 L1 OR L2
L4 = 541 S ASCORB?/AB
L5 = 9 S L3 AND L4
L6 = 1007378 S REDUC?
L7 = 14740 S PHOSPHIT? OR HYPOPHOSPHIT?
L8 = 9 S L4 (P) L5
L9 = 18 S L7 AND L3
L10 = 113 S L4(P) L6
L11 = 1141 S TECHNETIUM OR PERTECHNETATE
L12 = 1 S L10(P) L11
L13 = 340244 S (REDUCING OR REDUCTANT)
L14 = 89 S L3 AND (L13 (P) (COPPER OR CU OR ZINC OR ZN OR IRON OR FE))
L15 = 7 S L14 NOT L9
L16 = 176 S 534/14/CCLS AND L3
L17 = 17 S L16 AND PHOSPHIN?
L18 = 126 S L16 NOT (L14 OR L9)
L19 = 15 S L17 AND L13